Use of the IL-6R Antagonist Tocilizumab in Hospitalized COVID-19 Patients

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Keywords: COVID-19, tocilizumab, Interleukin-6; cytokine

Running title: Tocilizumab in COVID-19

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Dear Editor,

Severely ill COVID-19 patients have a high risk of admission to the intensive-care unit (ICU) and requirement for mechanical ventilation (MV), with in-hospital mortality reported as 18-79% globally.[1-4]. Among ICU patients in the United States (US), centers have reported 50% mortality.[5,6] Tocilizumab, an IL-6 receptor (IL-6R) antagonist, is FDA approved for the management of CAR T-cell related Cytokine Release Syndrome (CRS) and may have utility in treatment of some COVID-19 patients. We describe the clinical characteristics and initial outcomes of a cohort of patients treated with tocilizumab at the Swedish Medical Center in Seattle, Washington.

Methods

This retrospective cohort study included 42 adults (≥18 years old) hospitalized for COVID-19 and treated with tocilizumab at Swedish Medical Center (Seattle, USA) between March 16, 2020 and April 17, 2020. To provide context we identified a cohort of 41 matched patients not receiving tocilizumab. Patients enrolled in prospective clinical trials of tocilizumab were excluded from the study.

All data was abstracted from the electronic medical record and reviewed by a second investigator. Baseline patient demographic and clinical characteristics including severity of COVID-19 illness using the Chinese CDC definition were recorded up to 10 days prior to anti-cytokine therapy.[4] Clinical variables and major changes in clinical status such as admission to the ICU, initiation of MV, initiation of extracorporeal membrane oxygenation (ECMO), or death are described for 42 patients treated with tocilizumab. Survival and clinical outcomes were assessed for 42 tocilizumab-treated patients and 41 matched controls for whom at least 7 days of follow-up data were available or who had been discharged or died before 7 days following administration of tocilizumab or the corresponding time for the matched controls.

Continuous variables were expressed as median values with interquartile (IQR) or absolute ranges or means with standard deviations (SD). Categorical variables were described as a proportion of the total subjects in percentages. Spaghetti plots were constructed to show the course of various parameters with respect to time before and after administration of tocilizumab, and a

smoothing curve was fit to these data to show overall trends across time. Probability of discharge was summarized using cumulative incidence estimates, where death without discharge was treated as a competing risk. Analyses were performed with SAS version 9.4 software.

Informal comparisons were made to the matched controls simply as a means of providing context for the results observed among tocilizumab-treated patients. Controls who did not receive tocilizumab were matched 1:1 to tocilizumab-treated patients on exact World Health Organization (WHO) score at hospital admission and exact WHO score on the hospitalization day on which the matched tocilizumab patient received therapy (regarded as day 0 to correspond with day 0 of tocilizumab delivery). Day 0 and age were added to the matching algorithm with bands around perfect matching as follows: day 0 ± 5 days; age ± 10 years. Matching was performed in Stata v13.1 with calipmatch, using greedy matching without replacement.

Results

Forty-two patients with confirmed COVID-19 illness who met study eligibility and were treated with tocilizumab were identified. Forty-one matched controls not treated with tocilizumab were obtained. Demographic and clinical characteristics for both cohorts are shown in Supplement Table 1. The median age of tocilizumab-treated patients was 68 (range, 25-96). The median time from hospitalization to receipt of tocilizumab therapy was 4 days (IQR, 4) and similar between severely and critically ill patients. At the time of tocilizumab use, 21 (50%) patients had severe illness and 21 (50%) patients had critical illness (Supplement Table 1). Anti-viral therapy was present in 21 (50%) patients. Twenty-six (61.9%) patients were admitted to the ICU, 20 (48%) were mechanically ventilated, 17 (40%) were on vasopressors, and 2 (5%) were on ECMO (Figure 1G and 1H). The median length of follow-up for those who were alive and not discharged was 19 days (IQR, 5.5) for tocilizumab-treated patients and 11 days (IQR, 12) for matched controls.

Clinical and Laboratory Parameters

IL-6 levels prior to tocilizumab were available in 35 (83%) patients and demonstrated a mean IL-6 of 61 pg/mL (SD, 107) in severely ill patients and a mean of 342 pg/mL (SD, 783) in critically ill patients (Supplement Table 2). CRP exhibited a sustained improvement in all tocilizumab-treated patients over time (Figure 1C and 1D). The mean baseline CRP was 180 mg/L (SD, 96 mg/L) in severely ill and 237 mg/L (SD, 97 mg/L) in critically ill patients and decreased to mean levels of 11 mg/L (SD, 12 mg/L) and 9 mg/L (SD, 7 mg/L), respectively (Supplement Table 2). Positive

improvements in oxygenation were demonstrated in most severely ill patients (Figure 1E, Supplement Table 2). The median FiO2 at time of receiving tocilizumab was 50% (IQR, 64) with a median FiO2 of 28% at day 7 after tocilizumab in severely ill patients (Supplement Table 2). Improvements in oxygenation were also seen in patients with critical illness, though generally indicated by gradual decreasing FiO2 (Figure 1F).

Summary of Major Clinical Events in Tocilizumab-treated Patients and Controls

Among all tocilizumab patients, 7 (16.7%) were discharged and 9 (21.4%) died by day 7 after tocilizumab. At the time of last follow up, 23 (54.8%) have been discharged, 11 (26.2%) have died, and 8 (19%) remain hospitalized (Figure 1G and 1H). By day 7 after tocilizumab, 7 (33.3%) severely ill patients were discharged and 3 (14.2%) died (Figure 1G). At last follow-up 15 (71.4%) severely ill patients have been discharged, 4 (19.0%) died, with 2 (9.5%) remaining hospitalized (Figure 1G). Amongst severely ill patients, only 2 (9.5%) required MV after tocilizumab. One patient (4.8%) was liberated from the ventilator after 3 days while the other (4.8%) died after one day on MV. Amongst critically ill patients by day 7 after tocilizumab, none had been discharged and 6 patients (28.5%) had died (Figure 1H). At last follow-up 8 (38.1%) have been discharged, 7 (33.3%) died, with 6 (28.6%) remaining hospitalized (Figure 1H). Of the 20 critically ill patients requiring MV at time of tocilizumab use, 12 (60.0%) have been liberated from MV (Figure 1H). Two patients initially requiring ECMO, MV, and renal-replacement therapy have been discharged from the hospital and do not require ongoing renal-replacement therapy.

Among all matched control patients by day 7 (17.1%) were discharged and 11 (26.8%) had died. At last follow up, 10 (24.4%) were discharged from the hospital, 11 (26.8%) died, and 20 (48.8%) remain hospitalized at last follow up (Supplement Table 3). By day 7, 6 (28.6%) deaths and 6 (28.6%) discharges were observed in severe illness matched control patients. At last follow-up there remained 6 (28.6%) deaths and 8 (38.1%) severe illness control patients had discharged (Supplement Table 3) By day 7 in critical illness matched controls, 1 (5%) had been discharged and 5 (25%) patients had died (Supplement Table 3). At last follow up, 3 (15%) patients had been discharged and 6 (30%) patients had died (Supplement Table 3).

Discussion

In this retrospective cohort study, we report on use of tocilizumab in the treatment of severely and critically ill hospitalized COVID-19 patients. With follow-up to 7 days or more, discharge, or

death after tocilizumab use, we report improvements in laboratory parameters associated with hyper-inflammation and discharge from the hospital in 54.8%. Notably, in severe illness patients treated with tocilizumab, the rate of death by day 7 was less than in matched controls (14.2% vs 28.6%) with also slightly higher rate of discharge (33.3% vs 28.6%) in tocilizumab-treated patients, suggesting benefit of tocilizumab in the subgroup of severe illness patients. Mortality was similar overall in all tocilizumab-treated patients and control patients. In-hospital mortality for COVID-19 patients in China, Italy, and the US, ranges between 18% and 79%, with mortality varying by illness severity and combordities.[1,2,4-7] The overall mortality of our tocilizumab-treated patients was low in comparison to historical cohorts of hospitalized patients. For patients with severe illness, defined primarily by impairment in oxygenation, approximately 15-20% of historical patients required transfer to the ICU and/or MV.[2,3,7] In our series, only 9.5% of severely ill patients treated with tocilizumab required MV, with one patient since discharged from the hospital. Compared to historical cohorts of severely ill COVID-19 patients globally, our patients receiving tocilizumab may have lower rates of ICU transfer or initiation of MV than those who do not receive anti-cytokine therapy.

There are several limitations to our study. The study is observational and patients treated with tocilizumab in our series also received additional therapies for COVID-19 including hydroxychloroquine, Vitamin C, and anti-viral agents (Table 1). The contribution of these other therapies to the outcomes described here remains unclear. Additionally, the sample size presented here is relatively small with a short follow-up. Nonetheless, these data suggest that tocilizumab, an anti-cytokine intervention aimed at mitigating inflammation and cytokine storm, may improve outcomes for select patients with COVID-19 and warrants further study. Data from randomized controlled studies is awaited.

Notes

Authorship Contributions

KP and JMP designed and led the study, analyzed the data, created tables and figures, cared for patients, and wrote the initial manuscript. TG provided statistical analyses, analyzed the data, created tables and figures, and revised the manuscript. MB and NB collected the data, analyzed the data, and created tables and figures. JG and MH collected data, interpret data, cared for patients, and revised the manuscript. VD, JF, CM, SN, SB, AL, DSO, TW, JP, JM, and SY cared for patients and obtained data. TD, SM, KryP, JS, JR, and AI collected data.

Acknowledgments

The authors would like to thank all patients and their families participating in the study.

Potential conflicts of interest

KP declares consultation honoraria from Genentech, outside of the submitted work. JG reports grants from Merck, Viracor and Salix, outside the submitted work, and contracted research from Gilead, outside the submitted work. All other authors declare no competing interests.

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Figure Legends

Figure 1A-F. Serial Change in Temperature, CRP, and Oxygenation by Illness Severity in Tocilizumab-treated Patients. Panels A, C, E present data for Severe Illness Patients. Panels B,D,F present data for Criticial Illness Patients. (A, B) serial change in temperature, (C, D) serial change in CRP, and (E, F) serial FiO2. **Figure 1G-H. Clinical Status by Day Relative to Tocilizumab Treatment**. (G) Clinical status in severe illness patients and (H) Critical Illness Patients.

Figure 1: Serial Change in Temperature, CRP, and Oxygenation by Illness Severity in Tocilizumab-treated Patients